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Baseline perfusion alterations due to acute application of quetiapine and pramipexole in healthy adults

Michels, Lars ; Scherpiet, Sigrid ; Stämpfli, Philipp ; Herwig, Uwe ; Brühl, Annette B

Abstract: **BACKGROUND** The dopaminergic system is implicated in many mental processes and neuropsychiatric disorders. Pharmacologically, drugs with dopamine receptor antagonistic and agonistic effects are used, but their effects on functional brain metabolism are not well known. **METHODS** In this randomized cross-over, placebo-controlled and rater-blinded study, 25 healthy adults received an acute dose placebo substance (starch), quetiapine (dopamine receptor antagonist), or pramipexole (dopamine agonist of the non-ergoline class) 1 hour before the experiment. Background-suppressed 2D pseudo-continuous arterial spin labeling was used to examine whole-brain baseline cerebral blood flow (CBF) differences induced by the three substances. **RESULTS** We found that quetiapine reduced perfusion in the occipital (early visual areas) and bilateral cerebellar cortex relative to placebo. In contrast, quetiapine enhanced CBF (relative to placebo) in the striatal system (putamen and caudate nucleus) but also in the supplementary motor area (SMA), insular-, prefrontal- as well as in the pre- and postcentral cortex. Pramipexole increased CBF compared to placebo in the caudate nucleus, putamen, middle frontal, SMA, and brainstem (substantia nigra), but reduced CBF in the posterior thalamus, cerebellum, and visual areas. Pramipexole administration resulted in stronger CBF relative to quetiapine in the hypothalamus, cerebellum and substantia nigra. **CONCLUSIONS** Our results indicate that quetiapine and pramipexole differentially modulate regional baseline CBF. Both substances act on the dopaminergic system, although affecting distinct regions. Quetiapine altered dopaminergic function in frontal, striatal, and motor regions. In contrast, pramipexole affected CBF of the nigrostriatal (striatum and substantia nigra) dopaminergic, but less the fronto-insular system.

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REGULAR RESEARCH ARTICLE

Baseline Perfusion Alterations Due to Acute Application of Quetiapine and Pramipexole in Healthy Adults

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Abstract

Background: The dopaminergic system is implicated in many mental processes and neuropsychiatric disorders. Pharmacologically, drugs with dopamine receptor antagonistic and agonistic effects are used, but their effects on functional brain metabolism are not well known.

Methods: In this randomized crossover, placebo-controlled, and rater-blinded study, 25 healthy adults received an acute dose placebo substance (starch), quetiapine (dopamine receptor antagonist), or pramipexole (dopamine agonist of the nonergoline class) 1 hour before the experiment. Background-suppressed 2D pseudo-continuous arterial spin labeling was used to examine whole-brain baseline cerebral blood flow differences induced by the 3 substances.

Results: We found that quetiapine reduced perfusion in the occipital (early visual areas) and bilateral cerebellar cortex relative to placebo. In contrast, quetiapine enhanced cerebral blood flow (relative to placebo) in the striatal system (putamen and caudate nucleus) but also in the supplementary motor area, insular-, prefrontal- as well as in the pre- and postcentral cortex. Pramipexole increased cerebral blood flow compared with placebo in the caudate nucleus, putamen, middle frontal, supplementary motor area, and brainstem (substantia nigra), but reduced cerebral blood flow in the posterior thalamus, cerebellum, and visual areas. Pramipexole administration resulted in stronger cerebral blood flow relative to quetiapine in the hypothalamus, cerebellum, and substantia nigra.

Conclusions: Our results indicate that quetiapine and pramipexole differentially modulate regional baseline cerebral blood flow. Both substances act on the dopaminergic system, although they affect distinct regions. Quetiapine altered dopaminergic function in frontal, striatal, and motor regions. In contrast, pramipexole affected cerebral blood flow of the nigrostriatal (striatum and substantia nigra) dopaminergic, but less the fronto-insular system.

Keywords: arterial spin labeling, dopamine agonist, dopamine antagonist, quetiapine, pramipexole, cerebral blood flow

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Introduction

The brain's dopaminergic system has been implicated in a number of mental disorders, such as schizophrenia (Howes and Kapur, 2009) and depression (Dunlop and Nemeroff, 2007). Pharmacologically, dopamine (DA) receptor antagonists are primarily used in the treatment of psychotic and agitated symptoms, whereas DA D2 receptor agonists are approved mainly for treatment of Parkinson's disease (PD) and Restless Legs Syndrome, but have also been used as monotherapy and augmentative treatment in depression (Corrigan et al., 2000; Goldberg et al., 2004). Quetiapine (QT) acts as antagonist at the DA D2 receptor, as well as at the serotonin 2A (5-HT_{2A}) receptor (dose-dependent, besides additional effects at the H₁ and other 5-HT and adrenergic receptors). Specifically, QT is characterized by a high affinity for the 5-HT_{2A} receptor and a fast dissociation rate (and low affinity) for the DA D2 receptor (Kessler et al., 2006), although it has also been shown that QT can have a high (striatal) DA D2 receptor occupancy in some cases (Tauscher et al., 1997; Pavics et al., 2004). Based on these pharmacological targets, QT is used to treat patients with schizophrenia, bipolar disorder, autism, and depression (Wen et al., 2014). In contrast, pramipexole (PX) acts as a selective agonist on the DA D2 and D3 receptor (Kvernmo et al., 2006) and also shows antidepressant properties (Goldberg et al., 2004). Pharmacologically, DA D2, D3, and D4 receptors are clustered as DA D2-like receptors compared with DA D1 and D5 receptors (Stoof and Kebabian, 1981; Mansour and Watson, 2000; Neves et al., 2002). Overall, PX and QT have relatively good pharmacologically opposed mechanisms (except for the serotonergic and histaminergic actions of QT). Neuroanatomically, DA D2 receptors are primarily found in entorhinal, orbitofrontal, and insular cortical areas, and subcortically in the striatum (e.g., caudatum, putamen, nucleus accumbens, globus pallidum, and the ventral striatum), the central amygdala, and the substantia nigra and ventral tegmental area in the midbrain (Rosenkranz and Grace, 2002a, 2002b; Ott et al., 2014). DA D3 receptors are not found in neo- and paleocortical areas and the orbitofrontal region but are strongly represented in the nucleus accumbens shell and specifically the Islands of Calleja (Ridray et al., 1998). In schizophrenia, there is an ongoing debate whether functional and structural brain changes seen in patients are due to the disorder itself, an effect of antipsychotic treatment, or a combination of both (e.g., recent meta-analyses: Fusar-Poli et al., 2013; Haijma et al., 2013; Vita et al., 2015). Antipsychotic pharmacological effects are thought to rely primarily on DA receptor antagonistic effects. However, despite the known distribution of the receptors in the brain, the main places of action of dopaminergic drugs are not well characterized. A recent meta-analysis on pharmacological functional magnetic resonance imaging (fMRI) studies summarized the evidence for acute and chronic effects of antipsychotics (including QT) on the fMRI signal in cortical and also striatal and nigrostriatal regions (Roeder et al., 2013). For example, treatment with QT in healthy participants for 3 days increased functional connectivity of anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex with the amygdala during a virtual aggressive behavior task (Klasen et al., 2013). QT has been shown to increase the fMRI signal of the orbitofrontal lobe during emotional (Fahim et al., 2005; Stip et al., 2005; Mancini-Marie et al., 2006) and verbal fluency task processing (Jones et al., 2004) in patients with schizophrenia and one case report in depersonalization disorder treated for a period of several weeks.

DA agonists have been shown to increase prefrontal perfusion in rats (Nordquist et al., 2008) and in humans with schizophrenia (Mu et al., 2007).

One method to characterize basic pharmacological effects in the brain is (pseudo-continuous) arterial spin labeling (pCASL) MRI, which measures noninvasively cerebral blood flow (CBF) variations. Changes in CBF can not only be affected by localized brain activity, but also possibly by vascular effects due to dopaminergic and other receptors on glial cells and cerebral vasculature (Mandeville et al., 2013). In addition, changes in CBF can also be affected by pharmacological effects on the coupling between brain metabolism and the vascular reaction. We would expect such vascular effects of dopaminergic modulation to be rather homogeneously distributed, reflecting a direct vasodilatory effect on cerebral blood vessels, as observed for levodopa (Leenders et al., 1985) or DA per se (Sabatini et al., 1991; Krimer et al., 1998). One previous ASL study showed decrements in CBF in the prefrontal cortex (PFC) after 7-day treatment with amisulpride, an antagonist at D2/D3 receptors (Viviani et al., 2013). The acute application of amphetamines, however, which block the reuptake and thereby increase the levels of DA, lowers CBF in the nigrostriatal but not in the cortical system (Lavyne et al., 1977). This reduction was similar to the effect of increased endogenous DA release due to stimulation of the substantia nigra (Lavyne et al., 1977). A recent study using pulsed continuous ASL demonstrated acute effects of D2 antagonist and agonist on (resting) CBF in humans (Handley et al., 2013). Specifically, the authors reported increased CBF in the basal ganglia (putamen) after a single dose of haloperidol (D2 antagonist) and aripiprazole (D2 partial agonist). The CBF increase was more pronounced for haloperidol than for aripiprazole in the (right) putamen and in the striatum.

In parallel to amphetamines, PX decreased regional CBF, measured using Positron Emission Tomography (PET) in baboons, in orbital frontal cortex, thalamus, cingulate cortex, and insula, whereas it increased relative CBF was shown in the temporal poles, cerebellum, and visual cortex (Black et al., 2002).

In the current study, we aimed to characterize acute effects of dopaminergic agonistic and antagonistic modulation on CBF at rest to enable conclusions about the site of action under acute administration of dopaminergic drugs. We used pCASL in healthy adults to identify CBF changes after acute application of QT and PX compared with placebo. In a randomized way, all subjects were supplied (at 3 different days, each at least 1 week apart, similar day-times) with one of the following substances: QT, PX, or placebo, and underwent every time the identical MR scan protocol.

Based on the known specific and spatially widespread modulatory effects of QT and PX on DA D2 and D3 function, we hypothesize opposing effects of these drugs on CBF in the fronto-striatal and nigrostriatal system. Specifically, and based on previous reports (Handley et al., 2013), we expected to see increased CBF in the basal ganglia for QT and PX relative to placebo.

Methods

Participants

The sample consisted of 25 healthy volunteers (mean age: 27.6 years \pm 7.6 years, and range: 20–46 years; 13 females), although reliable pCASL could be achieved in only 23 subjects. All participants in this sample were right-handed (Annett, 1967). Exclusion criteria included any kind of metal implants or pacemakers; any history of medical disorders that pose risk to subjects (e.g., any allergy against medication; any acute or chronic somatic disorder [particularly affecting cardiac and vascular function]; pulmonary disease, neurological, psychiatric,

haematological, endocrine, or major genitourinary disease) or jeopardize the aim of the study by introducing confounds (e.g., prevalence of illicit drug usage, daily consumption of more than 2 alcoholic beverages, intensive cigarette smoking [>1 pack/d]) and heavy caffeine consumption). Participants were screened for current and previous mental disorders using the MINI interview (Sheehan et al., 1998).

The study protocol was approved by the institutional review board of the County of Zurich, Switzerland (KEK no. ZH-2009-0060) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent after full explanation of the procedures and received monetary compensation.

Drug Treatment

Each participant received 1 to 1.5 hours before each of the 3 scans a single dose of 100mg QT, 0.5mg PX, or placebo (starch tablet without any pharmacologically active ingredient, identical to the QT and PX tablets in size and color). The drugs were administered in a closed wrap. The dosages were chosen to avoid strong side effects such as hypotension and sedation (QT) and nausea (PX). The drugs were administered in a single-blind, randomized, crossover design. We do use the term “treatment” here for this single-dose design, but it should not be confused with longer term treatment protocols.

Acquisition of Structural Data

MR scans were acquired on a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) equipped with an 8-channel head coil. MR-compatible headphones were used to minimize head motion. A T1-weighted 3D-MPRAGE anatomical scan was recorded with the following parameters: time of repetition/time of echo: 8.3/3.8ms, flip angle: 8°, voxel resolution: $0.94 \times 0.94 \times 1$ mm, field of view: 240 mm, and 160 slices.

ASL Acquisition

CBF was measured with a 2D background-suppressed pseudo-continuous ASL (pCASL) sequence (Wong et al., 1997). PCASL was chosen because of its high signal-to-noise characteristics (Wu et al., 2007; Dai et al., 2008). The acquisition parameters were: time of repetition/time of echo: 4120/15ms, flip angle: 90°, field of view: 240mm, number of slices: 23, number of dynamics: 35, in plane resolution: 3×3 , thickness: 7 mm (no gap), labeling time: 1.65 seconds, postlabeling delay: 1.525 seconds, and scan duration: 4:56 minutes. Two background suppression pulses (at 1.68 and 2.76 seconds) were used. M_0 are the equilibrium brain tissue magnetization images (Wang et al., 2003a; Federspiel et al., 2006; Jann et al., 2010) and were recorded in a separate run for each participant immediately after the pCASL scan using the same parameters as described for the pCASL sequence apart from the time of repetition (10000 ms).

ASL Analysis

ASL images were preprocessed using the toolbox “ASLtbx” (Wang et al., 2008), which was compatible with MATLAB and the SPM software package (<http://www.fil.ion.ucl.ac.uk/spm/>), used for group comparison analysis. The first step was motion correction (Wang, 2012) and denoising. Subjects were excluded from subsequent analysis if any of the 3 (scan-to-scan) translation parameters exceeded one-half of the voxel size or if rotation values exceeded 1° (which was the case in 2 participants). This step was also important to minimize global signal outliers (spikes) during the calculation of perfusion signal by pairwise subtraction,

resulting from inconsistent background suppression or spatial location offset due to head motion. Next, we performed denoising, which included spatial smoothing with an isotropic Gaussian at full-width-at-half-maximum of 6mm³ to reduce interindividual anatomical differences and further increase the signal-to-noise ratio. Then, all nonbrain voxels were excluded using the Freesurfer software (relevant functions: ‘fslmerge’ to create a mean brain mask and ‘fslstats’ to remove nonbrain voxels).

As a next step, CBF quantification was performed using a single compartment model (Buxton et al., 1998; Wang et al., 2008), and its estimation is explained in the next paragraph. For the calculation of the perfusion difference images ($M_{\text{control}} - M_{\text{label}}$), simple pairwise subtraction (label–control) was used, as it has been demonstrated to efficiently minimize spurious BOLD contaminations within the CBF signal (Wang et al., 2003b; Liu and Wong, 2005). Furthermore, it has been demonstrated that simple subtraction in resting-state CBF data works with the same performance as special filtering approaches (Liu and Wong, 2005; Chuang et al., 2008). During CBF quantification, volunteer’s mean CBF maps were corrected for the (tissue-dependent) proton density derived from the M_0 image.

CBF Quantification

CBF was calculated on a voxel-wise basis according to the formula:

$$\text{CBF} = \frac{60 * 100 * \lambda * (M_{\text{control}} - M_{\text{label}})}{2\alpha T_{1\text{blood}} * M_0 \left(e^{\frac{-w}{T_{1\text{blood}}}} - e^{\frac{-w+\tau}{T_{1\text{blood}}}} \right)}$$

$M_{\text{control}} - M_{\text{label}}$ reflects the subtraction of label and control images, and λ = blood brain partition coefficient for water = 0.9 (Herscovitch and Raichle, 1985), $T_{1\text{blood}} = 1664$ ms (Lu et al., 2004), M_0 = equilibrium brain tissue magnetization images, τ = labeling pulse train length = 1.68 s, α = labeling efficiency = 0.85 (Dai et al., 2008), as background suppression was used, and w (posttagging delay) = 1.53 s.

The labeling efficiency and the T_1 of blood were taken from literature values, derived from previous experimental studies (Lu et al., 2004; Dai et al., 2008), and were part of the compartment model (see above) or entered as variables in the ASLtbx, respectively. The equilibrium magnetization of blood was calculated from the equilibrium magnetization of CSF and multiplied by a correction factor for T_2^* decay. The relevant blood H_2O partition coefficient was taken from the literature (Herscovitch and Raichle, 1985).

After CBF quantification, volunteers’ mean CBF map were normalized to the Montreal Neurological Image (MNI) template (average of 200 realigned brain images) to allow for statistical treatment comparisons (see below). The MNI template was provided by the SPM8.

Global CBF Calculation

First, a brain mask template was created for each subject to exclude all nonbrain voxels from the normalized CBF map (using the FSL software package, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Then, a mean whole-brain CBF map (i.e., uncorrected for partial volume effects) was calculated by averaging all voxels across all subjects. This map was used to show CBF variations across the whole brain for the different treatments (placebo, QT, and PX) on the group level. In addition, we used individuals’ global CBF values as confounding covariate at the voxelwise CBF analysis (see below).

Whole-Brain CBF Statistical Analysis

A general linear model (GLM), in our case a repeated-measures ANOVA, was applied using SPM8 to assess whole-brain CBF effects on the voxel-to-voxel level. CBF differences were estimated for 3 contrasts: “placebo – QT” (and reversed), “placebo–PX” (and reversed), and “QT–PX” (and reversed). First, we tested with for a main effect of treatment (placebo, QT, and PX). Next, we applied posthoc *t* tests to assess between-treatment effects. Whole-brain CBF differences are reported using a voxel-wise threshold of $P < .001$ ($t > 3.2$, uncorrected) or, for visualization purposes, $P < .005$ ($t > 2.66$, uncorrected). Only clusters > 10 voxels (> 0.63 mL) are shown. Additionally, we performed the same type of analysis, but this time we included individuals’ global CBF values as confounding covariate in the GLM. For cortical regions, CBF values are reported with corresponding anatomical names and Brodmann areas (BAs).

We also estimated the local CBF change for QT and PX relative to placebo, in regions showing the strongest difference, estimated as follows: $(\text{CBF QT [or PX]} - \text{CBF placebo}) / \text{CBF placebo} \times 100$ (to gain relative CBF changes in percent). To assess a global estimate of percent CBF differences, regions of interest (ROIs) were created using ROIs from the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), which hence included the local peak CBF between-treatment difference but also some surrounding intra-regional volume. Since it is known that particularly CBF in the basal ganglia is altered after treatment with D2 antagonists or agonists (Handley et al., 2013), we extended the ROI analysis to these regions, including the (right and left) putamen, caudate nucleus, and pallidum.

Finally, we tested whether voxelwise CBF treatment differences are the by-product of intra-treatment time-dependent CBF

changes. Here we first estimated within-treatment CBF maps for the first and second halves of the recording and then compared (by paired *t* tests) those sets of CBF maps. All statistical maps were examined on a rather exploratory statistical threshold of $P < .01$ (uncorrected) to not miss any drug-induced temporal CBF change.

Acquisition of Physiological Data

We recorded blood pressure and heart rate (beats per minute) before and after each pCASL scan. Additionally, we tested whether between-treatment differences remained stable if we included the blood pressure ratio (ratio systolic/diastolic value), mean arterial pressure (MAP), or heart rate as regressor of no interest in the GLM. The MAP was calculated according to $\text{MAP} = 2/3 \text{ diastolic} + 1/3 \text{ systolic value}$. The GLM was calculated separately for the effect of cardiac parameters using pre- and post-ASL scan values.

Results

Whole-Brain Analysis

Across all 3 treatments, whole-brain analysis revealed a main effect of treatment ($F = 7.8$, $P < .001$) with significant clusters in the right visual cortex (MNI *x/y/z*: 6/-80/12), left brain stem (MNI: -10/-10/-10), left prefrontal cortex (MNI: -40/54/20), and right cerebellum (MNI: 31/-64/-38). Global CBF maps for each treatment are shown in Figure 1, indicating (a) high-quality ASL recordings for all 3 treatments, and (b) the absence of any strong lateralization effects in the anterior-posterior, inferior-superior, or left-right direction.

As shown in Figure 2 and Table 1, the between treatment comparison revealed the following:

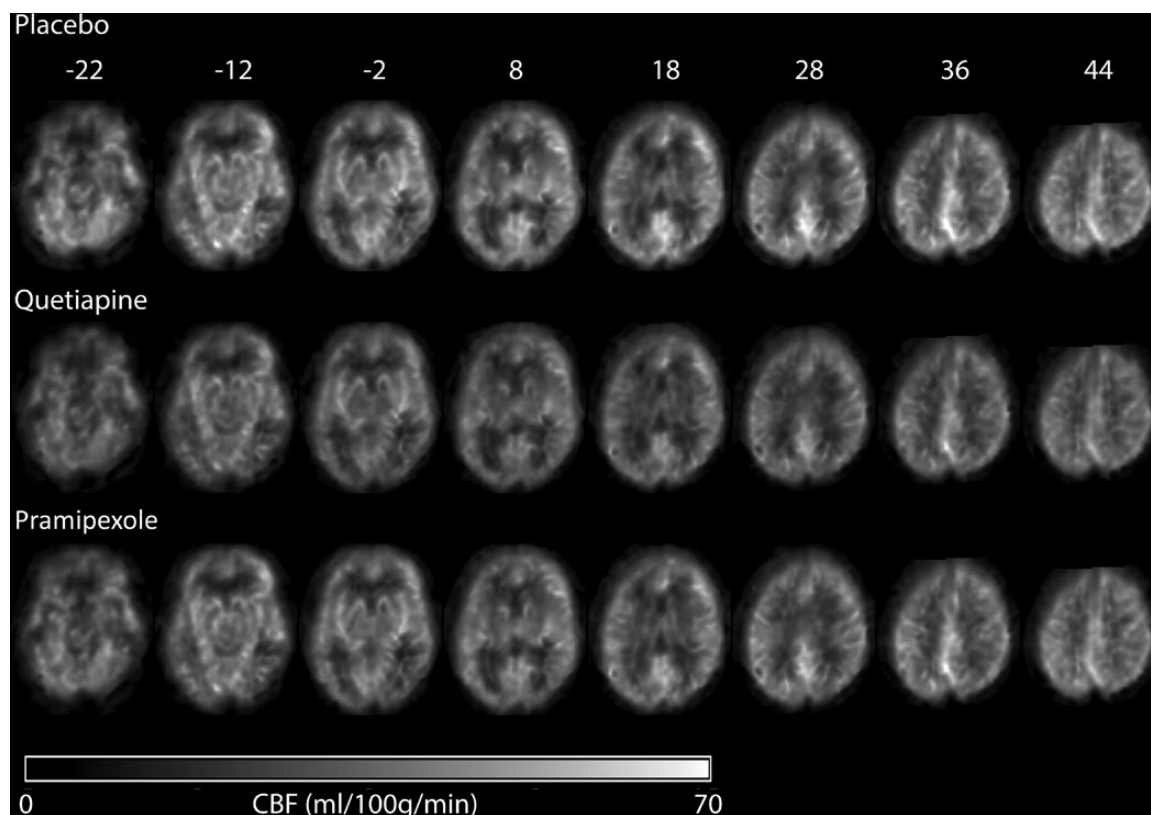


Figure 1. Whole-brain cerebral blood flow (CBF) maps for the 3 treatment groups: placebo (top), quetiapine (middle), and pramipexole (bottom). Lighter areas represent areas with higher CBF. CBF maps are shown on axial slices: range $z = -22$ to $z = 44$ (gap: 10mm) and are given in mL/100 g/min. The CBF maps reveal the absence of any strong lateralization effects in the anterior-posterior, inferior-superior, or left-right direction.

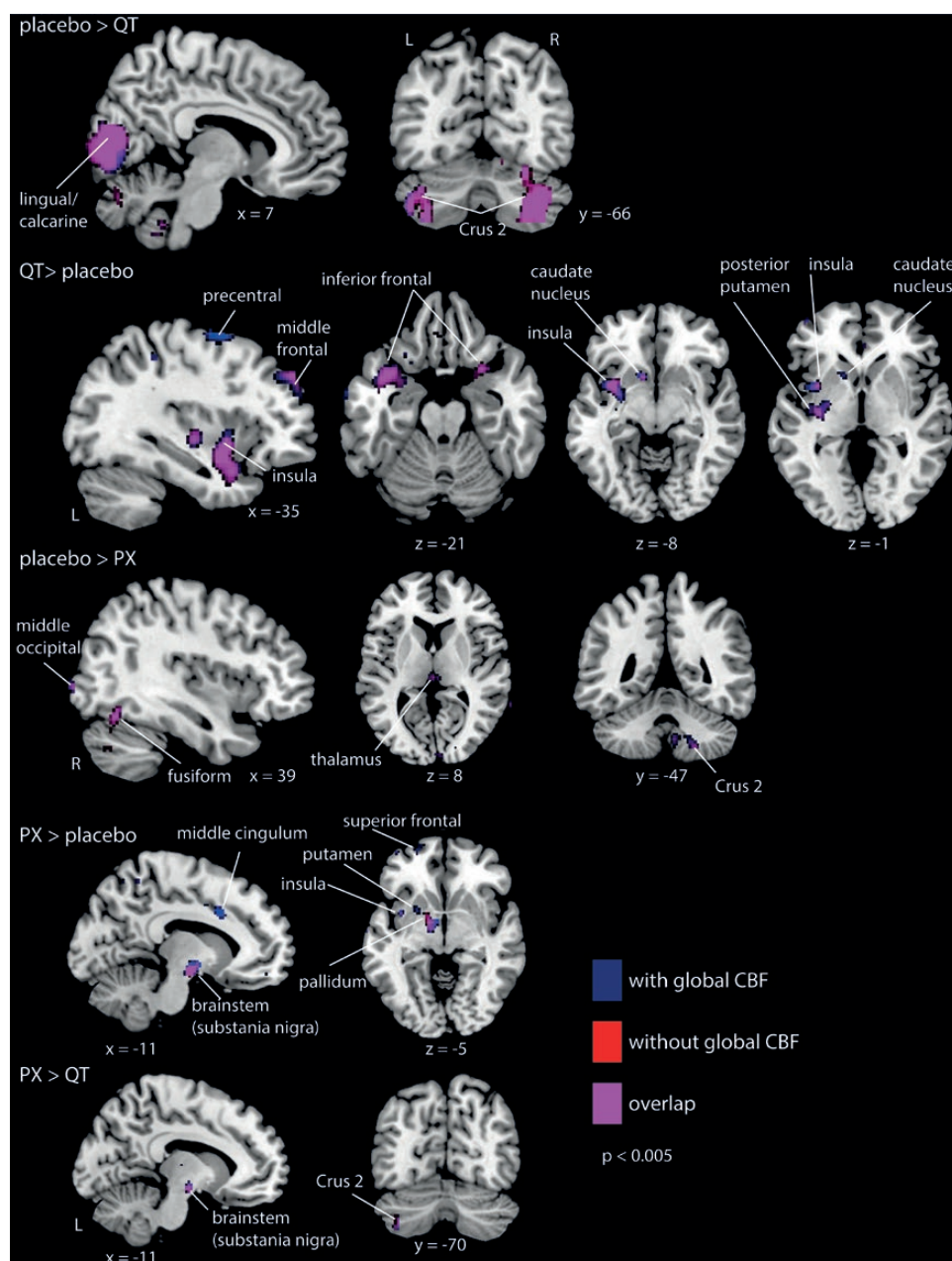


Figure 2. Statistical between-treatment cerebral blood flow (CBF) comparisons. All comparisons (placebo vs quetiapine [QT], QT vs placebo, placebo vs pramipexole [PX], PX vs placebo, and PX vs QT) are shown at a voxel-threshold $P < .005$ (uncorrected). Areas in blue denote changes in CBF with global CBF as confounding covariate in the statistical model. Areas in red indicate changes in CBF without global CBF as confounding variable in the analysis. Areas in pink show the spatial overlap between the 2 analyses. See Table 1 for the complete list of all significant CBF changes.

- QT reduced CBF relative to placebo, particularly pronounced in the bilateral visual cortex (19.05% CBF change), but also in the bilateral cerebellum (Crus 2) with a right hemispheric dominance.
- PX reduced CBF in the right cerebellum, thalamus, and fusiform cortex relative to placebo. If global CBF was included as confounding variable in the analysis, we found further decreases in CBF in the left fusiform gyrus, right cuneus, and superior temporal gyrus (global CBF was not significantly different between the treatments, all $P > .5$).
- QT increased perfusion relative to placebo in the left middle and right superior prefrontal cortex and left caudate nucleus and at the border of left posterior part of the putamen and

insular cortex (4% CBF change). If global CBF was included in the GLM, CBF was increased in left the pre- and postcentral gyri, bilateral inferior frontal orbital gyrus, right caudate nucleus, and right SMA.

- No CBF increases were detected when comparing QT with PX at $P < .001$ or $P < .005$.
- PX increased CBF relative to placebo in the bilateral caudate nuclei, left brainstem (including substantia nigra, 7% CBF change), and the left SMA and middle frontal gyrus (BA 11) if global CBF was included in the GLM.
- PX showed elevated CBF compared with QT in the left cerebellum and brainstem (including substantia nigra, 8% CBF change) and right hypothalamus.

Table 1. Treatment-Related CBF Differences

Contrast	Region (with Hemisphere) L: left, R: right	MNI Coordinates x/y/z	BA	t-Value	Cluster size
PX > QT	Cerebellum L (Crus 2)	-37 / -68 / -40		2.86	55
	Brainstem L (substantia nigra)	-7 / -12 / -12		2.82	35
^b QT > PX	Hypothalamus R	4 / -7 / -12		3.2	23
Placebo > QT	No significant clusters				
	Lingual gyrus L	-8 / -83 / -10	BA 18	3.26*	119
	Calcarine gyrus R	6 / -80 / 13	BA 17/23	3.96*	243
	Cerebellum L (Crus 2)	-34 / -73 / -44		3.68*	37
	Cerebellum R (Crus 1)	32 / -66 / -42		4.15*	249
placebo > PX	Cerebellum R (Crus 2)	24 / -78 / -43		3.07	144
	Fusiform gyrus R	40 / -66 / -18	BA 19	2.91	88
^b	Fusiform gyrus L	-35 / -78 / -16		2.7	43
	Thalamus L (medial dorsal nucleus)	-2 / -22 / 5		2.67	74
^b	Cuneus R	6 / -94 / 12		2.79	23
^b	Superior temporal gyrus R	71 / -26 / 13		2.74	33
QT > placebo	Middle frontal gyrus L	-42 / 54 / 16	BA10	3.84*	116
	Superior frontal gyrus R	47 / 35 / 40	BA 9	3.36*	23
^b	Postcentral gyrus L	-30 / -38 / 50	BA 40	2.95	43
^b	Precentral gyrus L	-24 / -10 / 65	BA 6	2.92	27
	Insula L	-38 / 3 / -2	BA 13	2.69	158 ^a
	Insula L	-37 / -14 / -3		2.99	158 ^a
^b	Inferior frontal orbital R	24 / 12 / -22	BA 47	2.95	33
	Inferior frontal orbital L	-31 / 14 / -20	BA 47	2.96	122
	Caudate L	-11 / 12 / -9		2.97	27
^b	Caudate R	11 / 15 / 15		2.86	24
	Putamen L	-30 / -16 / -4		2.8	66
^b	Putamen L	-12 / 12 / -7		2.94	49
	Supplementary motor area (SMA) R	4 / 25 / 58	BA 8	2.98	49
PX > placebo	Caudate R	20 / 21 / 12		3.30*	33
	Caudate L	-9 / 15 / 12		2.55	14
^b	Putamen L	-22 / 6 / -10		2.86	36
^b	Middle cingulum L	-5 / 6 / 44	BA 32	2.87	24
^b	Middle frontal gyrus L	-22 / 60 / -11	BA 11	2.8	15
	Brainstem L (substantia nigra)	-8 / -13 / -13		3.83*	29

Abbreviations: BA, Brodmann area; PX, pramipexole; QT, quetiapine.

Significance is reported at * $P < .001$ ($t > 3.2$) and $P < .005$ ($t > 2.66$).

^a Peaks within the same cluster.

^b Additional significant regions when including global CBF as confounding variable.

Figure 3 shows that pre- and post-pCASL scan differences were mostly comparable with respect to blood pressure (ratio systolic/diastolic) and heart rate. Differences were seen in (pre and post ASL scan) heart rate comparing placebo with QT (pre-pCASL: $P = .014$; post-pCASL: $P = .038$), with higher heart rates for QT. Further, placebo-related heart rate was lower before pCASL than after the pCASL scan ($P = .037$), which might be a result of getting up after lying down for 1.5 hours. Hence, we tested whether heart rate, blood pressure (ratio), or MAP had relevant effects on the observed between-treatment differences described above (and visualized in Figure 2 and Table 1). However, even at a very liberal statistical threshold of $P < .01$ (uncorrected), no CBF differences were seen when comparing the treatment-specific GLM excluding or including

either heart rate, MAP, or blood pressure (ratio) as regressors of no interest.

ROI Analysis

The ROI analysis (of the basal ganglia) demonstrated stronger CBF in the bilateral caudate nucleus and putamen (left-dominant) as well as in the left pallidum with both treatments relative to placebo (Figure 4, changes are indicated in %). Some of these increases were significant: QT vs placebo (left caudate nucleus: $P = .01$, $t = 2.67$; left putamen: $P = .02$, $t = 2.4$) and PX vs placebo (left putamen: $P = .04$, $t = 2.1$; left pallidum: $P = .1$, $t = 1.7$). Further, the CBF change in the left caudate nucleus was stronger (trend) for the contrast QT vs placebo than for PX vs placebo ($P = .07$, $t = 1.9$).

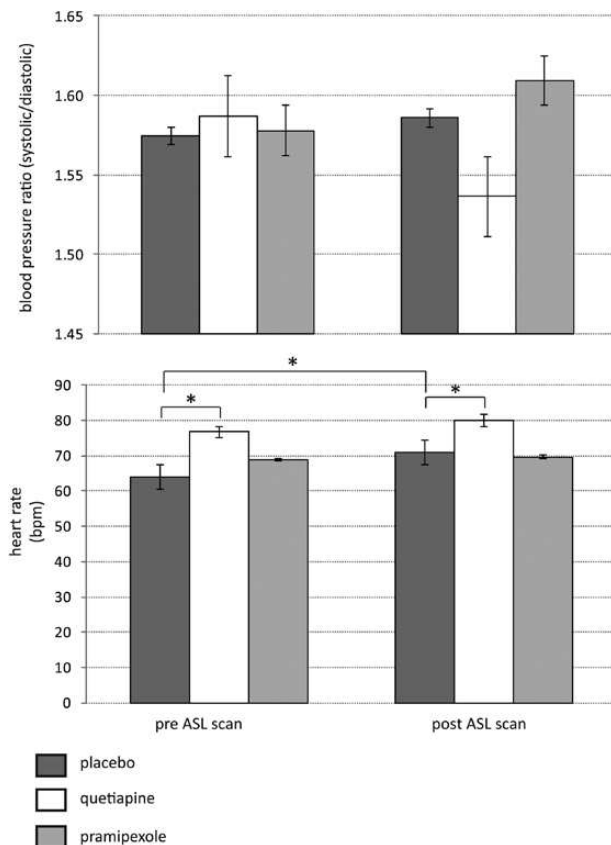


Figure 3. Cardiac response (blood pressure [ratio systolic/diastolic] and heart rate) before and after the (pseudo-continuous) arterial spin labeling (pCASL) scan. Between-treatment differences were mostly comparable for both time points. Yet, differences were seen in (pre- and post-ASL scan) heart rate comparing placebo with quetiapine (QT) (pre-pCASL: $P = .014$; post-pCASL: $P = .038$), with higher heart rates for QT.

Discussion

Main Findings

We found that a single acute application of both DA agonists and antagonists altered CBF (relative to placebo) in healthy adults in a localized manner. Specifically, QT increased prefrontal (including the basal ganglia) but reduced visuo-cerebellar CBF compared with placebo. In contrast, PX enhanced CBF in the nigrostriatal (brainstem at the level of the substantia nigra and caudate nucleus) system but reduced CBF in the thalamus, visual cortex, and cerebellum.

phMRI: The Value of ASL

The 2 primary methods in phMRI include BOLD contrast and ASL-MRI. Although the BOLD contrast has been widely used in phMRI studies (Abler et al., 2007, 2011, 2013; Bruhl et al., 2010, 2011; Rawlings et al., 2010), it has some weaknesses (no absolute quantification). In contrast, ASL-MRI has some advantages such as absolute quantification of CBF both at rest and during task activation and high reproducibility over minutes to weeks (Chen et al., 2011; Wang et al., 2011). Therefore, ASL can be an additional or even alternative tool for studying both i.v. and oral acute and longer term drug action as well as understanding drug effects on baseline brain function.

QT Effects on CBF

We found reduced CBF after QT intake in the early (calcarine and lingual) visual cortex and cerebellum (Crus 2) relative to placebo. In addition, we observed enhanced perfusion after QT in the left striatum (posterior putamen) and insular cortex as well as in other frontal regions such as the caudate nucleus, middle frontal gyrus (BA 10), and superior frontal gyrus (close to BA 11). However, we found no CBF differences in the ACC even at a liberal voxel

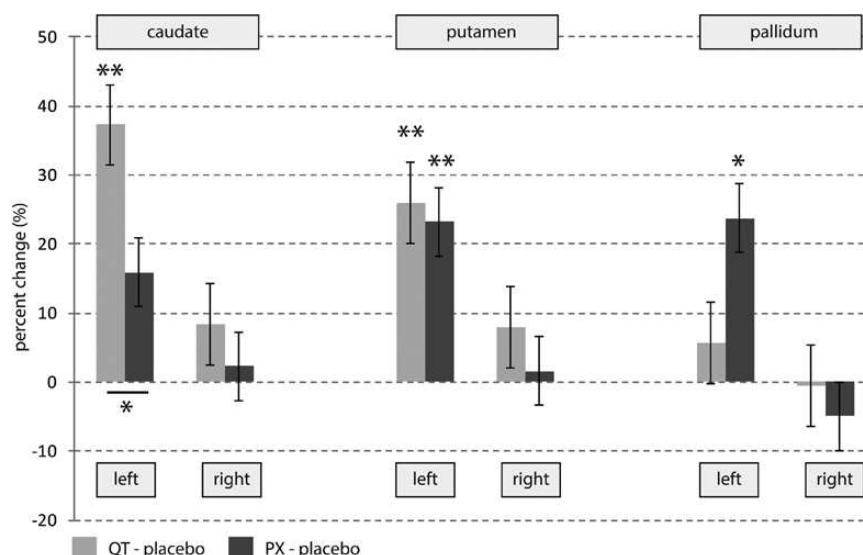


Figure 4. Region of interest (ROI) analysis. Percent change in cerebral blood flow (CBF) (%) with standard error is given for 2 contrasts: quetiapine (QT) vs placebo and pramipexole (PX) vs placebo. The analysis was performed in anatomically defined regions of the basal ganglia, including the (left and right) caudate nucleus, putamen, and pallidum. Significant differences due to medication (relative to placebo) and between medications are indicated by * $P < .1$ or ** $P < .05$. Apart from the right pallidum, both medications increased CBF (i.e., positive % change) compared with placebo.

threshold of $P < .005$ (uncorrected). QT acts primarily as an antagonist at the DA D2 receptor but is also an antagonist on 5HT_{2A}, 5HT_{1A} (partial), and H₁ histaminergic receptors. DA D2 receptors have a high density in the mesolimbic and nigrostriatal system (Camps et al., 1989), whereas DA D₁-receptors are mainly present in the cerebral cortex and cerebellum (De Keyser et al., 1988a, 1988b; Mansour and Watson, 2000). The nigrostriatal pathway includes the brainstem (clustered in the substantia nigra), ACC, caudate nucleus, and medial PFC. Previous PhMRI studies using ASL perfusion MRI have been conducted after application of the D2 receptor antagonist metoclopramide (Fernandez-Seara et al., 2011). In a placebo-controlled study in healthy volunteers, a single oral dose of metoclopramide increased CBF bilaterally in the striatum (putamen), consistent with its DA D2 receptor antagonism, and reduced CBF in the insular cortices and anterior temporal lobes. In our study, we found for the DA D2 receptor antagonist that QT increased CBF compared with placebo in the (posterior) putamen and caudate nucleus but increased in the insular cortex. One reasonable explanation for this finding might be that QT acts differently on the DA D2 receptors than metoclopramide, as both substances have a differential receptor profile (additional M1 acetylcholine receptor agonistic effect in metoclopramide). The antagonistic effect of QT on 5HT_{2A}, 5HT₁ (partial), and H₁ histaminergic receptors (all present in the insular cortex; <http://human.brain-map.org/>) could explain this difference, which is also supported by the lack of a strong effect of PX in this region.

Dopaminergic reward signals have been shown to modulate the BOLD signal in the visual cortex, that is, gating sensory plasticity (Arsenault et al., 2013). We suggest that the impact of QT on prefronto-striatal DA receptor function (enhanced CBF) is paralleled by reduced CBF in the occipital cortex, maybe as a result of lower control mechanisms of the PFC. The occipital cortex contains both 5HT_{1A} and 2A receptors (Allen Brain Atlas, <http://www.brain-map.org>), which could suggest a direct serotonergic effect of QT in these regions. However, we found similar effects in the occipital cortex after PX administration (see below), which rather supports a dopaminergic modulatory effect of QT on the occipital cortex. Another explanation for the reduction of CBF in the visual cortex might be the effect of QT on vigilance, potentially mediated by the antihistaminergic effect of QT. Yet this is less likely, as neither blood pressure nor heart rate was lower after QT relative to placebo intake (Figure 3).

The increased CBF in the motor cortex (SMA and precentral gyrus) after treatment with QT in our study corresponds to another study in healthy individuals (Handley et al., 2013) and in patients using haloperidol (Lahti et al., 2009), which would support a particular D2 receptor antagonism effect in this region.

Effects of PX on CBF

Pharmacologically, PX acts specifically on DA D2 receptors. PX reduced in our study occipital and thalamic CBF, and we noticed a consistent (PX > placebo and PX > QT) increase of perfusion in the brainstem, specifically in the substantia nigra. This suggests that PX affects predominantly the nigrostriatal system compared with the more cortico-striatal effects seen with QT.

In rodents, a prior study investigated DA D2 effects using aripiprazole, an antipsychotic, acting as DA D2 receptor partial agonist. Using CASL, the study reported a dose-dependent decrease in brain perfusion in the entorhinal piriform and perirhinal cortex, nucleus accumbens shell, and basolateral amygdala (Nordquist et al., 2008). Our results with PX show a different modulation pattern in the brain focused on the nigrostriatal and the limbic network.

The major afferent innervation of the basal ganglia is derived from the cortex and thalamus (Kemp and Powell, 1971a, 1971b). In our study, PX reduced CBF in thalamus relative to placebo. This region heavily connects to the striatum and other parts of the basal ganglia (McFarland and Haber, 2002). Specifically, these excitatory inputs from the thalamus mainly target the striatum, where they innervate the principal type of striatal neuron and are critical in the expression of basal ganglia function (Huerta-Ocampo et al., 2014). In schizophrenia patients, high levels of DA have been reported in the thalamus (Oke et al., 1988), and since then it has been discussed whether this area is critical to the pathophysiology of schizophrenia (Moghaddam, 2010). Indeed, our data lend support for a common but anticorrelated modulatory effect of PX on CBF within the thalamo-nigrostriatal (brainstem) system. This suggests that antipsychotic drugs (at least with DA agonism) can modulate CBF as they might modulate dopaminergic function. Interestingly, aripiprazole, which is a partial D2 agonist/antagonist, had no modulatory effect on CBF in the thalamus in a recent ASL study in healthy individuals (Handley et al., 2013). This discrepancy between the 2 studies could be due to the partial antagonistic effect of aripiprazole.

In addition to a D2 receptor-mediated effect, PX has also been shown to decrease intracellular DA contents, potentially mediated by effects on PX production and the vesicular DA uptake (Izumi et al., 2008). In our study, the acute oral application of PX resulted in a CBF increase in the midbrain (substantia nigra), which is consistent with its clinical use in PD (review in Fox et al., 2011) and other disorders involving the nigrostriatal motor system (e.g., tremor severity in Holmes' tremor; Seidel et al., 2009) in humans and in normalizing cellular and motor dysfunctions in PD-affected rats (Jeon et al., 2007; Shin et al., 2009). Our analyses point towards a modulatory role of QT and PX on the striatal system. Yet, effects turned out to be more widespread when we considered global CBF as a covariate of interest in the statistical analysis (Figure 2; Table 1). This observation is in line with a recent study (using pulsed continuous ASL) in healthy volunteers, who found fewer CBF changes (after treatment with antipsychotic drugs) when global CBF was not included as a covariate (Handley et al., 2013). Since global CBF did not differ among the selected treatment regimes, this result indicates that (without its inclusion) small inter-subject physiological CBF differences may have hampered the identification of region-specific at the whole-brain (group) level.

Limitations

Our study has some limitations. The main limitation is that we had to use rather low dosages of both drugs to avoid side effects such as nausea (PX) and sleepiness/sedation (QT), which both would have interfered with the testing. For PX, we would not expect any major differences in terms of receptor occupancy when using higher dosages. For QT, however, some studies show a more prominent 5HT as well as noradrenergic receptor affinity in lower dosages and a stronger dopaminergic effect in higher dosages, but binding studies show a comparable affinity for D2 and 5HT_{2A} receptors (Richelson, 1999; Nemeroff et al., 2002). One PET binding study showed relevant DA D2 receptor occupancy even at low plasma levels in healthy controls (Nord et al., 2011), and 2 other PET studies suggest that possibly both the DA D2 and the 5HT_{2A} receptor occupancy increase with increasing dose of QT (Kapur et al., 2000; Gefvert et al., 2001). However, other treatment studies show both a prominent cortical binding to 5HT_{2A} receptors (Rasmussen et al., 2011) and a predominant striatal binding to dopaminergic receptors (Pavics et al.,

2004) even at rather low therapeutic doses. Thus, we cannot be absolutely certain about the pharmacological specificity of the QT effects alone. Yet, when combining the QT DA-antagonistic results with the more specific PX DA-agonistic results, we can draw more certain conclusions about DA-specific effects. One other limitation is that we have no individual plasma level measurements, which could explain some lack of sensitivity of our study; when controlling for interindividual plasma level differences, we could have achieved more information about plasma level dependent variation. Due to the possibly varying receptor profile depending on the single dosage and with repeated dosages, future studies might want to look at dose-dependent effects of QT on CBF, possibly in addition measuring plasma levels to correlate with the CBF variation. In addition, we did not record baseline ASL prior to any treatment. Therefore, we cannot exclude any placebo effects on CBF. However, the placebo effect on CBF should not be locally uniform and specific across participants, and the direct contrast between PX and QT should control for potential placebo effects on regional CBF.

One important aspect, although not a limitation, is that this study cannot be directly compared with studies investigating the effect of longer term treatment in patients or healthy subjects, because these longer term intake studies are measuring direct pharmacological and more indirect adaptive effects due to the treatment.

Conclusion

Our results indicate that the main regions where CBF was differentially modulated by QT and PX, suggesting rather specific dopaminergic effects, were substantia nigra, cerebellum, and hypothalamus. Other regions such as prefrontal and subcortical areas showed elevated CBF after intake of both QT and PX, although with a more prominent effect of QT on prefronto-striatal network compared with a midbrain-striatal network modulated by PX. This suggests on the one hand certain specific dopaminergic effects of QT, but also differences compared with other DA receptor antagonist (e.g., metoclopramide) and DA D2 agonists (e.g., PX), possibly as a result of different receptor profiles.

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Statement of Interest

None.

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